



REVIEW PAPER

EFFECT OF SELENIUM SUPPLEMENTATION IN THYROID GLAND DISEASES

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ABSTRACT

Selenium, a non-metal chemical element, is present in the human body in trace quantities and accumulates mostly in the thyroid gland. Selenium-rich food includes offal, meat and meat products, seafood, milk and dairy products, yeast, and bread. The aim of the study is to collate and discuss research results obtained over the last 13 years regarding the influence of selenium in diseases of the thyroid gland. Selenium deficiency can lead to a number of thyroid diseases. Over 30 proteins containing selenium called selenoproteins, and their numerous functions in the human body, have been identified. Research shows that selenium is essential for proper synthesis, activation and metabolism of thyroid hormones. It also can postpone the development of hypothyroidism, reduce the level of anti-thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), normalize thyroid echogenicity in ultrasound examination, improve the condition of patients with Graves' disease and autoimmune thyroiditis (AIT) (Hashimoto's thyroiditis), and reduce the incidence of postpartum thyroid dysfunction. The recommended dose of selenium for adults is 45-55 $\mu\text{g 24 h}^{-1}$ (Polish recommendations) or 55 $\mu\text{g 24 h}^{-1}$ (recommendations in the US). Selenium may have a toxic effect in doses above 400 $\mu\text{g 24 h}^{-1}$; therefore a threshold of 400 $\mu\text{g 24 h}^{-1}$ has been adopted as the maximum safe dose. The role of selenium supplementation in diseases of the thyroid gland is still subject to discussion.

Keywords: selenium, thyroid, autoimmune thyroiditis, Graves' disease, Hashimoto's thyroiditis, goiter.

INTRODUCTION

Selenium is a chemical element that was discovered by J.J. Berzelius in 1817. Its atomic number is 34, and it is in group 16 and period 4 of the periodic table. It produces significant toxicity if oversupplied and, due to numerous side effects, it has not been used in medicine for many years. Research carried out in recent years has confirmed that selenium is essential for human life.

Selenium is enclosed in proteins known as selenoproteins (RAYMAN 2000). More than 30 of these proteins have been identified, of which the best known are forms of glutathione peroxidase (for example: GPx1, GPx2, GPx3 and GPx4) (important antioxidants), and three forms of iodothyronine deiodinase (a catalyst in the production of thyroid hormones and regulator of their level). Other selenoproteins include selenoprotein P, which protects endothelial cells against damage from peroxynitrite and transports selenium to the peripheral organs, selenoprotein W, required for muscle function, and selenophosphate synthetase 2 (SPS2), the precursor of selenocysteine and an essential component of selenoprotein synthesis (RAYMAN 2000). Selenoprotein P is essential in selenium homeostasis and is a major biomarker of selenium in human plasma (TURANOV et al. 2015). Being a component of the enzyme (thioredoxin reductase), selenium is involved in the recovery of ascorbic acid from its oxidized metabolites. It also plays a role in the cell growth and transformation as well as the in protection against oxidant injury (MUSTACICH, POWIS 2000).

Selenium enters the human body through consumption of food crops. Shellfish, Brazil nuts, and the liver and kidneys of animals are rich in selenium (Table 1). People absorb selenium from plants in the form of amino acids: selenomethionine and selenocysteine (FINLEY 2006). Selenomethionine may be incorporated into the body's proteins by replacing methionine, and in this manner selenium is stored in human tissues (SCHRAUZER 2003). The con-

Table 1
Approximate content of selenium in selected food products (from www.foodcomp.dk)

Food product	Approximate content of Se ($\mu\text{g } 100 \text{ g}^{-1}$)
Kidney, pig, raw	182
Brazil nuts	103
Liver, pig, raw	47.6
Asian tiger shrimp: prawn, giant tiger, aquaculture products, boiled, frozen	32.1
Salmon	31.5
Herring, raw	24.5
Eggs, chicken, free-range (outdoor) hens, raw	22.2
Buckwheat groats, raw	20.0

tent of selenium in plants primarily depends on the amount of this element in soil, which varies depending on a geographic region. Soils of Central and South America have relatively little selenium, therefore the inhabitants of these areas are exposed to mild regional selenopenia. In contrast, the soils of North America contain large amounts of this element (NAVARRO-ALARCON, CABRERA-VIQUE 2008). In Central Asia (Tibet and Lhasa), where selenium levels are very low, the local villagers suffer from severe selenopenia, manifested as Keshan disease (a cardiomyopathy characterized by fulminant heart failure) or Kashin-Beck osteochondropathy. A necessary condition for the development of Keshan disease is a viral infection inducing oxidative stress, i.e. the presence of a virus Coxsackie B that in the deficiency of selenium is converted to a cardiotoxic form (MORENO-REYES et al. 1998). European soils have varied levels of selenium. For example, Polish soils are low in this element (average value 0.27 mg g^{-1}). In northern Europe, studies have shown a suboptimal selenium content in soil (ČUVARDIĆ 2003).

The recommended nutrient intake of dietary selenium is $55 \text{ } \mu\text{g } 24 \text{ h}^{-1}$ ($0.7 \text{ } \mu\text{mol } 24 \text{ h}^{-1}$), the US recommendations (RAYMAN 2008). The Institute of Food and Nutrition recommends $45\text{-}55 \text{ } \mu\text{g } 24 \text{ h}^{-1}$ selenium for the Polish population (JAROSZ M. et al. 2012). This recommendation was based on assessment of the plateau of selenoprotein glutathione peroxidase (Gpx) activity in the plasma. The recommended intake is the amount of selenium required for the maximum synthesis of this enzyme. The Tolerable Upper Intake Level for adults is set at $400 \text{ } \mu\text{g } 24 \text{ h}^{-1}$ ($5.1 \text{ } \mu\text{mol } 24 \text{ h}^{-1}$), with selenosis being the manifestation of the toxic effect of selenium (US Institute of Medicine 2000).

Organic forms of selenium are safer than inorganic forms for human supplementation. Unassimilable selenomethionine and selenite contained in supplements are broken down into volatile selenium excretion products, for example dimethylselenide (DMSe) and dimethyldiselenide (DMDS₂), in the caecum and colon (KRITTAPHOL et al. 2011). Selenium toxicity (selenosis) is manifested as fatigue, diarrhoea, fingernail discoloration, nausea, hair loss, joint pain and brittleness of nails and hair (MACFARQUHAR et al. 2010). There have also been reports suggesting that long-term dietary supplementation with this element at a dose of $200 \text{ } \mu\text{g } 24 \text{ h}^{-1}$ increases the risk of development of type 2 diabetes (hazard ratio: 2.7) (STRANGES et al. 2007). However, this study was conducted in an area with a high content of selenium in the soil. Studies in China show that high levels of plasma selenium in a Chinese population are associated with a metabolic syndrome and elevated fasting plasma glucose (YUAN et al. 2015).

In this paper, the latest scientific reports on the effects of selenium supplementation in the thyroid gland diseases was presented.

MATERIAL AND METHODS

The following electronic databases for all levels of evidence pertaining to selenium and thyroid gland diseases were searched.: PubMed, Web of Science, Cochrane Library and Medline. A keyword approach was used, combining clinical (thyroiditis, thyroid) and therapeutic (selenium) search terms: “Selenium,” “Selenium thyroid,” “Selenium Hashimoto,” “Selenium thyroiditis,” and “Selenium autoimmune thyroiditis.” The search was conducted in July 2015 and September 2015. The screening of reports was initially based on a review of titles. When in doubt, abstracts and/or full texts were reviewed as well. Only English language publications were included.

Studies were categorized as “positive” or “negative.” The term “positive” designates studies that found beneficial effects of selenium supplementation in thyroid diseases, while „negative” indicates studies that found neither significant beneficial effects nor any evidence of harm. In the absence of reported levels of significance, the authors’ interpretation was used to guide classification.

RESULTS AND DISCUSSION

The greatest concentration of selenium in the human body has long been known to be located in the thyroid gland (DICKSON, TOMLINSON 1967). In conditions of deficiency of this microelement, the thyroid retains more selenium than the brain (SCHWEIZER, SCHOMBURG 2005). This is probably because the thyroid gland produces selenoprotein P locally in cases of reduced selenium in the diet (SCHOMBURG, KÖHRLE 2008).

Selenium is an essential element for the proper functioning of all isoforms of iodothyronine deiodinase, an enzyme regulating the conversion of thyroxine (T₄), triiodothyronine (T₃) and reverse triiodothyronine (rT₃). Selenocysteine present in the enzyme removes iodine residues contained in the hormones of the thyroid gland. Graves’ disease and hypothyroidism are marked by pathological expression of type II iodothyronine deiodinase, which precedes clinical symptoms of these diseases (KÖHRLE et al. 2005). Severe endemic deficiency of selenium combined with iodine deficiency has also been shown to lead to endemic myxedematous cretinism, reported in northern Zaire (VANDERPAS et al. 1990).

Studies have shown that selenium deficiency can cause thyroid diseases (LACKA, SZELIGA 2015, WU et al. 2015). Other investigations show that in patients with euthyroidism selenium has little effect on the TSH and fT₄ level (which decreases slightly) compared to those taking a placebo, as no significant effect of selenium supplementation was detected on plasma fT₃ or the fT₃ / fT₄ ratio. This suggests that selenium should not be used as a supplement when there is only a minimal deficiency of this element (WINTHER et al. 2015). The results of recent studies on the effect of selenium supplementation on thyroid function are presented in Table 2. The cited reports do not

Table 2

Results of studies conducted over the past 13 years concerning the influence of selenium on thyroid function in adults

Category	Author	Disease	Study group		no. of patients and age	treatment	Control group		Description	Time	Results
			no. of patients and age	treatment			no. of patients and age	treatment			
1	2	3	4	5	6	7	8	9	10		
Positive	DE FARIAS et al. (2015)	autoimmune thyroiditis	28, age 20-58 years	selenomethionine 200 µg 24 h ⁻¹	27, age 21-56 years	placebo	randomized placebo-controlled	3 months	in study group 5% reduction of the level of anti-thyroid peroxidase antibodies (TPOAb) at 3 months and 20% at 6 months; no changes in placebo group.		
Negative	MAO et al. (2014)	pregnant women from a mild-to-moderate iodine-deficient population	115, adults	60 µg 24 h ⁻¹ Se-yeast	114, adults	placebo	randomized placebo-controlled	from 12 to 35 week of gestation	No bigger effect than placebo in decreasing TPOAb concentration or the prevalence of TPOAb positivity during the course of pregnancy.		
Positive	MARCOCCI et al. (2011)	Graves' disease, mild Graves' orbitopathy	54, age 43.0±11.0 years	200 µg 24 h ⁻¹ Na ₂ SeO ₃	50, age 44.6±10.7 years	placebo	randomized placebo-controlled	12 months (6 months of treatment and 6 months follow-up)	After 6-month treatment improved quality of life was noted alongside less ocular involvement and slow progression of Graves' orbitopathy (as compared with placebo). Exploratory evaluations at 12 months confirmed the results seen at 6 months.		

cont. Table 2

1	2	3	4	5	6	7	8	9	10
Positive	NACAMULLI et al. (2010)	autoimmune thyroiditis	46, age 17-75 years	$80 \mu\text{g } 24 \text{ h}^{-1}$ Na_2SeO_3	30, age 27-63 years	no treatment	cross-sectional	12 months	Thyroid echogenicity decreased significantly in both groups after 6 months, but after 12 months dropped further only in the placebo group. TPOAb decreased after 12 months (no changes after 6 months in both groups).
Negative	KARANIKAS et al. (2008)	autoimmune thyroiditis	18, adults	L-thyroxine LT4, $200 \mu\text{g } 24 \text{ h}^{-1}$ Na_2SeO_3	18, adults	LT4, placebo	randomized placebo-controlled	3 months	No difference between study and control groups.
Positive	MAZOKOPAKIS et al. (2007)	Hashimoto's thyroiditis	80, age 24-52 years	$200 \mu\text{g } 24 \text{ h}^{-1}$ selenomethionine	-	-	prospective	12 months two steps lasting 6 months several	After first 6 months TPOAb decreased by 9,9%.
			40, adults	continue taking $200 \mu\text{g } 24 \text{ h}^{-1}$ selenomethionine	40, adults	stopped taking selenomethionine			An overall reduction TPOAb by 21% (after year) in study group; increase of 4.8% in control group.
Positive	NEGRO et al. (2007)	positive for thyroid peroxidase antibodies	77, age 28 ± 6 years	selenomethionine $200 \mu\text{g } 24 \text{ h}^{-1}$ during pregnancy and the postpartum period	74, age 28 ± 5 years	placebo (81 women without TPOAb was control group, they did not take either selenium or placebo)	randomized placebo-controlled	9 months gestation	Occurrence of permanent hypothyroidism and postpartum thyroid dysfunction was significantly lower in study group than in placebo group (11.7% vs. 20.3% and 28.6% vs. 48.6%).

cont. Table 2

1	2	3	4	5	6	7	8	9	10
Positive	TURKER et al. (2006)	autoimmune thyroiditis,	48, age 40.8 ± 12.5 years	LT4, selenomethionine 200 µg 24 h ⁻¹	40, age 39.2 ± 14.4 years	LT4, placebo	randomized placebo-controlled	9 months three steps lasting 3 months several	No changes in placebo group; in study group TPOAb level decreased by 26.2%.
			20, adults	continue LT4, selenomethionine 200 µg 24 h ⁻¹	20, adults	LT4, patients who initially received selenium took selenomethionine 100 µg 24 h ⁻¹			TPOAb decreased in 200 µg 24 h ⁻¹ selenium group by 23.7%, increased significantly in 100 µg 24 h ⁻¹ selenium group by 38.1%.
			12, adults	continue LT4, selenomethionine 200 µg 24 h ⁻¹	12, adults	LT4, patients who received 100 µg 24 h ⁻¹ selenium took selenomethionine 200 µg 24 h ⁻¹			No significant changes in group which took 200 µg 24 h ⁻¹ TPOAb level decreased by 30.3% after increase of selenium dose from 100 µg 24 h ⁻¹ to 200 µg 24 h ⁻¹ .
Positive	VRCA et al. (2004)	Graves' disease	29, more than 60% were 30-45 years	methimazole, supplementation with vitamins C and E, beta-carotene and 60 µg 24 h ⁻¹ selenium (the authors did not describe the forms of selenium)	28; more than 60% were 30-45 years	methimazole	randomized	2 months (30 days of treatment and 30 days of follow-up)	Patients who received supplementation with antioxidants developed euthyroidism faster than patients treated with methimazole only.
Positive	DUNTAS et al. (2003)	autoimmune thyroiditis,	34; adults with median age 48 years	selenomethionine 200 µg 24 h ⁻¹ , LT4 to maintain TSH levels between 0.3-2.0 mU l ⁻¹	31; adults with median age 48 years	LT4, placebo	randomized placebo-controlled	6 months	TPOAb levels decreased by 55.5% in study group and by 27% in control group.

cont. table 2

1	2	3	4	5	6	7	8	9	10
Positive	GÄRTNER et al. (2002)	autoimmune thyroiditis,	36; age 41.6 ± 12.1 years	LT4, 200 µg 24 h ⁻¹ Na ₂ SeO ₃ ,	34; age 41.6 ± 12.1 years	LT4, placebo	randomized placebo-controlled	3 months	TPOAb levels decrease of 36.4% in research group (60% at TPOAb >1200 IU ml ⁻¹) and of 22% in control group (10% increase at TPOAb >1200 IU ml ⁻¹); 9 patients in the study group had completely normalized antibody concentrations, in contrast to 2 patients in the placebo group. Ultrasound of the thyroid showed normalized echogenicity in these patients.
Positive, continue research from 2002	GÄRTNER, GASNIER (2003)	autoimmune thyroiditis,	13 Se-Se group, age 27-56 years	LT4, patients which initially received selenium continued to take 200 µg 24 h ⁻¹ Na ₂ SeO ₃	9 Se-0 group, age 27-56 years	LT4, patients stopped taking selenium	randomized placebo-controlled	6 months	TPOAb decreased from 625.0 ± 470.0 U ml ⁻¹ to 354.0 ± 321.0 U ml ⁻¹ (by 55% in Se-Se group and increased from 450.0 ± 335.0 to 708.0 ± 313.0 U ml ⁻¹ (by 55%) in Se-0 group.
			14 0-Se group, age 27-56 years	LT4, patients which received placebo before started to take 200.0 µg 24 h ⁻¹ Na ₂ SeO ₃	11, age 27-56 years	LT4, without selenium supplementation			TPOAb decreased from 1182.0 ± 723.0 to 643.0 ± 477.0 U ml ⁻¹ (by 54%) in 0-Se group, no changes in placebo group.

provide information about the dietary supply of selenium received by the patients with thyroid disorders. The content of selenium in a diet has an effect on its concentration in the serum and can affect test results (FRIEDRICH et al. 2011). The results of studies on selenium supplementation in thyroid diseases are not conclusive in terms of improving patients' health. The cited reports have shown that mean levels of thyroid-stimulating hormone TSH, free thyroxine (fT4), and free triiodothyronine (fT3) were unchanged in the control and experimental groups (GÄRTNER et al. 2002, GÄRTNER, GASNIER 2003, DUNTAS et al. 2003, TURKER et al. 2006, MAZOKOPAKIS et al. 2007, KARANIKAS et al. 2008, NACAMULLI et al. 2010, DE FARIAS et al. 2015).

Research on the occurrence of endemic goiter in the province of Hatay (in Turkey) has shown that we should look for selenium and zinc deficiency in patients with endemic goiter. The prevalence of selenium deficiency has been found to be higher than that of iodine deficiency in patients with endemic goiter (ÇELİK et al. 2014). However, in most of the known cases, the main cause of endemic goiter was iodine deficiency. Selenium and iodine supplementation in diffuse goiter was more effective than administration of iodine alone. For this reason, 100 micrograms of selenium per day together with iodine can be recommended for treatment and prevention of diffuse goiter in cases of selenium and iodine deficiency (OSADTSIV et al. 2014). Some studies suggest that selenium deficiency can affect the development of thyroid cancer (GLATTRE et al. 1989, MONCAYO et al. 2008), but other reports contradict this assumption (SHEN et al. 2015). Low selenium levels have also been shown to cause autoimmune processes within the thyroid gland; therefore selenium deficiency may contribute to Graves' disease and to autoimmune thyroiditis (LACKA, SZELIGA 2015). Selenium supplementation in autoimmune thyroiditis can reduce the level of anti-thyroid peroxidase antibodies (TPOAb) in the blood serum (GÄRTNER et al. 2002, GÄRTNER, GASNIER 2003, DUNTAS et al. 2003, TURKER et al. 2006, MAZOKOPAKIS et al. 2007, NACAMULLI et al. 2010, DE FARIAS et al. 2015) and normalize echogenicity in ultrasound examination (GÄRTNER et al. 2002). A dose above 100 μg 24 h^{-1} is needed to achieve a significant effect. The suppression rate has been found to decrease with time, but only in one study (TURKER et al. 2006). This study also concluded that selenium supplementation may accelerate the occurrence of remission in Graves' disease and reduce orbitopathy occurring in this disease (MARCOCCI et al. 2011). A decreased serum concentration of selenium in pregnant women with hyperthyroidism compared with healthy women confirmed the hypothesis that hyperthyroidism is associated with reduced antioxidant response (ARIKAN 2015). Selenium supplementation (200 μg 24 h^{-1}) during pregnancy and in the postpartum period reduced thyroid inflammatory activity and the incidence of hypothyroidism (NEGRO et al. 2007). Studies in a spontaneous autoimmune thyroiditis model of mice have shown that treatment with selenium increases the level of selenoproteins and reduces the level of thyroglobulin antibodies in plasma (WANG et al. 2015).

CONCLUSIONS

Selenium reduces the concentration of TPOAb. Current guidelines of the Polish Society of Endocrinology do not indicate the need for selenium supplementation in thyroid diseases, despite the positive studies mentioned in this paper. Administration of selenium to pregnant women with elevated TPOAb titers is not recommended. The benefits of selenium supplementation demonstrated through tests must be verified by further research into the mechanisms of action of selenium compounds in the immune system. The genetic background of patients may also play an important role.

Long-term dietary supplementation with physiological doses of selenium ($80 \mu\text{g } 24 \text{ h}^{-1}$) seems to be effective in preventing a reduction in thyroid echogenicity and in reducing TPOAb and thyroglobulin antibodies (TgAb). Selenium may be much less effective in areas where it is abundant in soil (as well as in food) in comparison with areas where it is deficient. As selenium can postpone the development of hypothyroidism, extended tests should be carried out to determine who should be treated on the basis of TPOAb levels.

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